Disorders of consciousness after severe brain injury: therapeutic options

Caroline Schnakers[a] *and Martin M. Monti*[b,c]

Purpose of review
Very few options exist for patients who survive severe traumatic brain injury but fail to fully recover and develop a disorder of consciousness (e.g. vegetative state, minimally conscious state).

Recent findings
Among pharmacological approaches, Amantadine has shown the ability to accelerate functional recovery. Although with very low frequency, Zolpidem has shown the ability to improve the level of consciousness transiently and, possibly, also in a sustained fashion. Among neuromodulatory approaches, transcranial direct current stimulation has been shown to transiently improve behavioral responsiveness, but mostly in minimally conscious patients. New evidence for thalamic deep brain stimulation calls into question its cost/benefit trade-off.

Summary
The growing understanding of the biology of disorders of consciousness has led to a renaissance in the development of therapeutic interventions for patients with disorders of consciousness. High-quality evidence is emerging for pharmacological (i.e. Amantadine) and neurostimulatory (i.e. transcranial direct current stimulation) interventions, although further studies are needed to delineate preconditions, optimal dosages, and timing of administration. Other exciting new approaches (e.g. low intensity focused ultrasound) still await systematic assessment. A crucial future direction should be the use of neuroimaging measures of functional and structural impairment as a means of tailoring patient-specific interventions.

Keywords
coma, thalamocortical system, therapeutic intervention, traumatic brain injury, vegetative state

INTRODUCTION

Recent advances in neurocritical care have greatly increased the number of individuals who survive severe brain injury. Many patients go on to make significant cognitive and physical recovery, eventually returning to a relatively (or fully) independent lifestyle. Some patients, however, fail to fully recover a state of consciousness – defined in the clinic as the joint presence of arousal (i.e. cycles of eye-opening and closing) and awareness (e.g. voluntary responsiveness) – and enter, transiently or permanently, a disorder of consciousness (DOC) such as coma, the vegetative state, and the minimally conscious state (MCS) [1]. In addition to the devastating effects on the quality of life of patients themselves, these conditions are known to pose great emotional and financial strain on families, increase burnout rates in caregivers, and give rise to difficult ethical discussions [2–5], making the development of effective therapeutic intervention all the more important and pressing.

A FRAMEWORK FOR THERAPEUTIC INTERVENTION IN DISORDER OF CONSCIOUSNESS

The recent surge in the development of potential therapeutic interventions for DOC patients (see Table 1 for an overview) is tributary to significant advances in our understanding of the biology of these conditions. In particular, Schiff *et al.* [6] have recently re-framed DOC as a 'disconnection syndrome' in which a, functional and/or structural, circuit-level disruption of a cortico-striatopallido-thalamocortical

[a]Research Institute, Casa Colina Hospital and Centers for Healthcare, Pomona, [b]Department of Psychology and [c]Brain Injury Research Center (BIRC), Department of Neurosurgery, University of California Los Angeles, Los Angeles, California, USA

Correspondence to Martin M. Monti, PhD, Department of Psychology, University of California Los Angeles, Los Angeles, CA 90095, USA. Tel: +1 310 825 8546; e-mail: monti@ucla.edu

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KEY POINTS

- To date, there is a paucity of therapeutic options for patients who survive severe TBI but failing to fully recover consciousness.
- Currently, the best studied approaches are pharmacological (e.g. Amantadine) and neurostimulatory (e.g. tDCS).
- Many other exciting new developments exist (e.g. LIFU), but lack systematic and rigorous investigation capable of ruling out spontaneous recovery.
- The next phase of this field should include the use of neuroimaging techniques as a means of better stratification of patients and personalization of therapeutic interventions.

mesocircuit impairs the re-emergence of conscious responsiveness, a view supported by numerous recent lines of evidence [7▪▪,8–11,12▪]. Under this model, wherever sufficient neural tissue is available, behavioral, pharmacological, and neurostimulatory upregulation of certain mesocircuit nodes (e.g. cortex, striatum, thalamus) and/or downregulation of others (e.g. globus pallidus) could lead to a recovery of circuit-level function and, thus, behavioral expression.

BEHAVIORAL APPROACH

Sensory stimulation programs have a long history of being used in neurorehabilitation post severe traumatic brain injury (TBI), based on the idea that enriched environments benefit neural plasticity and, thereby, recovery [13▪,14]. In animal models, sensory stimulation via enriched environment is known to have important cellular manifestations [15] and to exert positive biological and behavioral effects after TBI specifically [16,17], putatively by restoring the excitation/inhibition balance in a layer-dependent fashion [18▪]. In humans, several studies investigated the impact of sensory stimulation programs on the recovery of DOC patients. Most, however, are noncontrolled designs or descriptive single cases. Recently, a crossover treatment design was employed to assess the effectiveness and biological correlates of familiar auditory sensory training (i.e. biographically relevant stories narrated by familiar voices) in a chronic TBI patient [19▪]. Administration of 40 min of stimulation over 6 weeks increased behavioral responsiveness, compared with baseline, in 3 out of 4 biweekly assessments. In the subsequent 6-week sham period, only two of the four biweekly assessments remained above baseline. Although small, effects were just above the threshold for minimum detectable change for the DOC scale (DOCS-25) [20]. Previous work by the same group has also documented, in a double-blind randomized placebo-controlled trial with 15 TBI patients, behavioral improvements following unimodal auditory stimulation [21]. Although the DOCS-25 changes were lower than those seen in the placebo group, a marginally significant effect was observed whenever using the coma/near-coma scale (CNC) [22]. Interestingly, compared with baseline, greater neuroimaging activations were observed in the treatment group, supporting the behavioral findings. In the acute context, a similar crossover design was applied in nine TBI coma patients to compare direct auditory stimulation (i.e. personally relevant, directed, and familiar sounds) with nondirect stimulation (i.e. nonpersonally relevant, directed, or familiar sounds) [23]. Although both types of stimulation resulted in increased arousal compared with baseline, the

Table 1. Summary of interventions discussed and time postinjury assessed in each investigation

Intervention	Acute/subacute time-point	Chronic time-point
Behavioral		
Sensory stimulation	21, 23	19
Music therapy	25, 26, 29	25, 26, 29
Pharmacological		
Amantadine	31, 32, 38	39, 40, 41
Zolpidem	47	42, 46, 48, 49, 50, 51
Neurostimulatory		
Deep brain stimulation (DBS)	59	61, 62, 63
Transcranial magnetic stimulation (TMS)	n/a	65, 66
Transcranial direct current stimulation (tDCS)	70, 73, 77	70, 71, 73, 76, 77, 78
Low intensity focused ultrasound (LIFU)	79	n/a

changes were significantly greater after direct stimulation.

Music therapy has also been used in severe TBI patients, given its well known therapeutic effects on patients with neurodegenerative (e.g. Alzheimer or Parkinson) and developmental (e.g. autism) disorders [13▪,24]. A number of studies suggest that music can enhance arousal and attention in DOC patients, as compared with white noise, disliked music, and 'nonmusical' auditory stimuli [25–28]. In a recent study, seven DOC patients underwent such a protocol in a crossover design comparing improvisational music stimulation responsive to patient behavior with background acoustic stimulation [29]. Although no differences were observed using the Coma Recovery Scale – Revised (CRS-R), music therapy-specific changes were noted, for both vegetative state and MCS patients, in the auditory responsiveness domain.

Overall, contradictory results exist for sensory stimulation paradigms [13▪,14,30], warranting further research, in much larger cohorts.

PHARMACOLOGICAL APPROACH

The use of Amantadine, a well known dopaminergic agent, is correlated with higher functional outcome and lower mortality among severe TBI patients [31–33]. Amantadine increases the availability of dopamine in the striatum by delaying its reuptake at the presynaptic level [34] and increasing the number of dopaminergic receptors at the postsynaptic level [35] – releasing (central) thalamic neurons from tonic pallidal inhibition [36,37]. A double-blind, randomized, placebo-controlled, multicenter study constitutes so far, the highest level of evidence for the use of Amantadine in promoting recovery after TBI [38]. The intervention lasted 6 weeks and included 184 vegetative state or MCS subacute patients randomly assigned to receive Amantadine or placebo. Functional recovery (e.g. recovery of consistent response to commands, intelligible verbalization) occurred earlier in the Amantadine group than in the placebo group, with no increase in the risk of adverse events (e.g. seizures). Using time-series designs, preliminary electrophysiological studies indicate a modulation of the alpha frequency bands [39,40], whereas one neuroimaging study showed a modulation of fronto-temporo-parietal and sensorimotor networks in response to treatment [41].

Zolpidem is an imidazopyridine, which acts as an agonist on subtype 1 of the inhibitory gamma-aminobutyric acid ($GABA_A$) receptor. Although the mechanisms of action of Zolpidem are not yet entirely clear, it is believed to affect the activity of cells in the globus pallidus, perhaps through a very specific selectivity for $GABA_A$ omega-1 receptors [42▪], resulting in a reduction of inhibitory pallidothalamic tonic activity and thus, a disinhibition of corticopetal (and striatopetal) thalamic neurons [6]. Zolpidem was initially used for its sedative, anticonvulsive, anxiolytic, and myorelaxant effects. Many studies have now reported the transient awakening effect of Zolpidem among vegetative state and MCS patients with traumatic (and nontraumatic) brain injuries [43▪,44]. Two double-blind placebo-controlled study reported significant recovery such as increased movement, social interaction, command following, and functional object use, but only in about 5% of a large sample of chronic DOC patients [45,46]. In a recent study, it was shown that in vegetative state patients not suffering from primary or secondary brainstem damage, administration of Zolpidem significantly ameliorated brain function and perfusion in brain-damaged regions, as compared with a placebo group [47]. Electrophysiological studies have documented an increase in beta frequencies and a decrease in alpha frequencies after Zolpidem administration [48,49], whereas neuroimaging studies have shown changes in frontoparietal and limbic regions [50,51]. The rapidity of the electrophysiological and metabolic effects of Zolpidem are noteworthy and make this approach clinically very appealing, particularly if its effects can be sustained over time [42▪]. Despite its low rate of effectiveness, its safety profile and the potential for remarkable behavioral recovery make its administration pragmatically sound, prior to attempting other potentially more effective but longer regimens. From a scientific point of view, the data so far certainly warrant further systematic exploration of its effectiveness with respect to causes of brain injury, lesion location, optimal time of administration (postinjury), effect duration, and mechanism of action [43▪,44].

Other drugs such as Levodopa [52,53] and Apomorphine [54,55], which are dopaminergic agents, and Baclofen, which is an agonist agent of the $GABA_B$ receptors [56–58], have also shown some beneficial effects on consciousness recovery in patients with severe brain injuries. Nevertheless, none of these studies formally controlled for natural recovery.

NEUROSTIMULATION APPROACH

The potential of neurostimulation as a restorative treatment after TBI has received increased attention over the past 10 years. In acute patients, a study of 21 patients (out of 107 considered) documented remarkable behavioral recovery, by 10–13 months

post TBI, after thalamic deep brain stimulation (DBS), including the ability to communicate [59]. DBS is a U.S. Food and Drug Administration (FDA)-approved technique in which a stimulator is implanted in a target brain region, which is then excited or inhibited via electric pulses [60]. In the context of DOC patients, the target region is typically central thalamus, which, whenever upregulated, is expected to lead to a functional restoration of mesocircuit activity and thus increased behavioral responsiveness. Schiff *et al.* [61] also reported treatment-related behavioral improvements, including the ability to communicate, in a chronic posttraumatic MCS patient after DBS to intralaminar thalamic nuclei. A more recent study reported a 7-year prospective, multiinstitutional, clinical trial, of DBS in DOC patients [62▪▪]. Out of 40 patients considered for the study, 35 did not meet criteria (mostly because of excessive anatomical damage) and, of the remaining 5, only 3 could undergo the procedure. All the three patients exhibited long-lasting improvements in responsiveness (averaging 1.67 points on the CRS-R at 6 months and 3 points after 18 months – which remained stable up to 4 years) and experienced improvement with respect to the severity and frequency of myoclonus and spasticity. Electrophysiological recordings also demonstrated a DBS-dependent increase in EEG frequency and desynchronization. Nonetheless, these results are overall sobering considering that over 87% of evaluated patients failed to meet very minimal inclusion criteria for DBS (comparable with the 80% exclusion rate of Yamamoto *et al.* [59]), one patient had to get the probe removed early because of infection, and that no patient recovered communication (unlike previous reports [59,61,63]). In all, given the present data, and given the fact that patients surviving severe TBI can undergo significant recovery well into the subacute phase post TBI [64▪▪], which might explain some of the reports (e.g. [59,63]), it is unclear whether the benefits of DBS outweigh its risks.

Alternative forms of neurostimulation, and particularly noninvasive approaches, have also been explored, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). TMS employs magnetic stimulation via a magnetic field generator, or 'coil', which is placed near the head of the patient receiving the treatment and is thought to induce action potentials and firing of otherwise resting neurons. TMS of the primary motor cortex has been applied in a traumatic MCS patient 5 years postinjury using a time-series design in which the examiner was blinded to the stimulation received (either TMS or median nerve stimulation as placebo). Behavioral changes such as response to command, object reaching, and object manipulation were observed after TMS administration (but not after placebo) [65]. As shown in a recent small-sample study, single-pulse TMS can exert very different effects on brain oscillations in DOC patients, compared with healthy volunteers [66], perhaps as a function of the underlying integrity of thalamocortical circuits – which might explain the exciting results of combined TMS-EEG in detecting levels of consciousness [67]. tDCS represents a well tolerated, cheap and user-friendly treatment that can be easily implemented in a rehabilitation setting. It is thought to induce membrane potential changes, modulations of N-Methyl-D-aspartate receptors efficacy as well as modification of ion channels (e.g. calcium) by decreasing or increasing the action potential threshold using a weak direct current (usually $\leq$ 2 mA) between two electrodes, the anode (i.e. excitatory) and the cathode (i.e. inhibitory) [68,69]. Thibaut *et al.* [70] have recently investigated the efficacy of tDCS in 55 DOC patients (including both vegetative state and MCS) using a double-blind sham-controlled crossover design. In this study, one tDCS and one sham session were administered over the dorsolateral prefrontal cortex. Significant behavioural increases were observed after tDCS, as compared with sham, in MCS patients, but not in vegetative state patients. At 1-year poststimulation, no difference in functional outcome was observed between responders and nonresponders, suggesting an effective, but transient, impact of single tDCS doses on recovery [70]. In a follow-up study, the effect of multiple (i.e. five) anodal tDCS stimulations, delivered over a week, was assessed in a group of 16 MCS patients. Significant behavioural improvements were observed, compared with sham, after the last dose. Importantly, however, the effect was observed to persist for (at least) a week [71▪▪]. Using multimodal neuroimaging analyses, Thibaut and co-workers showed that consciousness improvements after tDCS are related to grey matter integrity and/or residual metabolic activity in the thalamus, the medial prefrontal cortex and the precuneus, which is consistent with the critical role of cortico-thalamocortical loops in recovery after severe brain injury [6,72–74,75▪]. Similarly, oscillatory tDCS (to the cerebellum) has been shown to transiently affect, in MCS patients only, theta-band and gamma-band power, in parallel to behavioural performance [76]. A very recent double-blind study, however, challenges the effectiveness of cortical tDCS in more chronic DOC patients [77], consistent with the suggestion that time postinjury might be an important determinant of the effectiveness of the approach [78].

Finally, a recent case study reported the first use of thalamic low intensity focused ultrasound (LIFU)

stimulation as a neurostimulatory intervention in an acute DOC patient recovering from severe TBI [79▪▪]. LIFU employs low-energy sound waves to allow noninvasive, transient, and well tolerated excitatory or inhibitory stimulation of a target region (potentially) anywhere in the brain. The neurostimulatory effects of LIFU on neural tissue have long been shown in in-vitro tissue cultures, nonhuman animal models, and very recently, in humans [80]. Although the exact cellular and molecular mechanisms remain unclear, a popular hypothesis proposes that conformational changes in mechanosensitive membrane-spanning proteins, because of sound-induced tissue compression, tension, and/or sheering, lead to transmembrane ionic fluxes, which in turn, lead to changes in the membrane-resting potential and activation of ionotropic voltage-gated (Na^+, Ca^{++}, and K^+) channels [81,82]. LIFU has several advantages as compared with other neurostimulatory approaches. Like DBS (and unlike tDCS and TMS), it is capable of directly stimulating thalamic tissue. Conversely, like tDCS and TMS (and unlike DBS), it is entirely noninvasive. Furthermore, LIFU stimulation produces no detectable sound or sign that it is being delivered, thereby effectively blinding participant and experimenter. In the one reported case in which thalamic LIFU was used in a postcoma patient (who fulfilled behavioural criteria for MCS), increased behavioural responsiveness was observed within 24 h postsonication, as assessed with the CRS-R. By 3 days, the patient had regained language comprehension and appeared fully oriented [79▪▪]. This result was expected based on DBS thalamic stimulation in DOC patients [61,62▪▪] and LIFU thalamic stimulation in rodents, which has been shown to reduce the time-to-emergence of voluntary movement after ketamine–xylazine anaesthesia [83], and is in line with the mesocircuit model. Nonetheless, even though a second severe TBI patient has also shown behavioural amelioration after thalamic LIFU (M.M. Monti, personal communication), spontaneous recovery [64▪▪] should not be ruled out.

CONCLUSION

Overall, the evidence concerning Amantadine, Zolpidem, and tDCS is – to date – the most convincing. Amantadine has been well validated, in high-quality clinical studies, and has demonstrated good effectiveness in traumatic DOC patient. The work on Zolpidem is also of high quality, but has revealed a somewhat underwhelming effectiveness rate. Finally, tDCS is the best validated neurostimulatory approach and shows good short-term effectiveness in MCS patients, but remains to be further explored in terms of effect persistence and effectiveness in chronic patients. All other approaches await systematic investigation in larger samples properly controlling for spontaneous recovery [64▪▪]. The next phase of this field should include, alongside systematic large-sample controlled investigations, definition of the optimal administration timing of each intervention and the integrated use of neuroimaging to tailor interventions vis-à-vis each therapy's putative mechanism of action and patient-specific patterns of brain abnormality (e.g. [11,12▪,75▪]).

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Conflicts of interest

There are no conflicts of interest.

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